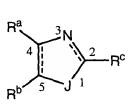
This listing of claims will replace all prior versions, and listings, of claims in the application:

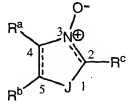
Listing of Claims:

1. (Presently Amended) A method of, in an animal, including a human, treating (i) diabetes or treating or ameliorating (ii) adverse sequelae of diabetes, (iii) kidney damage, (iv) damage to blood vasculature, atherosclerosis, peripheral vascular disease, coronary heart disease or heart failure, (v) hypertension, (vi) retinopathy, (vii) peripheral neuropathy, (viii) cataracts, (ix) osteoarthritis, (x) rheumatoid arthritis, (xi) Alzheimer's disease, (xii) damage to a tissue caused by contact with elevated levels of reducing sugars or (xiii) stroke, or (xiv) improving the elasticity or reducing wrinkles of the skin of an animal or (xv) increasing RBC deformability, comprising inhibiting the formation of, or reversing the preformation of, advanced glycosylation end products by administering an effective amount of a compound of formula I or IA,



I

or



IA

wherein:

a. J is oxygen, sulfur, or N-R^d;

b. the carbon 2 to nitrogen bond is a double bond except when R^c is oxo;

c. the bond between carbons 4 and 5 is a single bond or a double bond;

d. R^a and R^b are

2 1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, piperazin-1-yl, Ar {wherein, consistent with the rules

of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a substituted benzene, pyridine, pyrimidine, pyridazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, ArO-, $ArSO_2$-, ArSO1, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R_1 and R_2 comprise methylenedioxy-; or

2. together with their ring carbons form a C_6- or C_{10}- aryl fused ring; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including a fused double bond of the containing group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom O or S and zero to two atoms of N; or

5. together with their ring carbons form a fused five to eight membered second heterocycle, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, and $S(O)_n$, wherein n is 1 or 2;

~~b~~ **e.** R^d is alkyl, alkenyl, hydrogen, or Ar;

~~e~~ **f.** R^c is

1. oxo (when $\Delta^{2,3}$ is not present), or (when $\Delta^{2,3}$ is present) hydrogen, alkyl, alkylthio, hydrogen, mercapto, amino, amino(C_1-C_5)alkyl, amino(C_6 or C_{10})aryl, or wherein the amino of the last three groups can be substituted with

(a) Ar,

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z- , wherein Z is a carbonyl or $-SO_2-$

(c) formyl or alkanoyl, or

(d) up to two alkyl,

2. $-NHC(O)(CH_2)_n$-D-R^eR^f, wherein D is oxygen, sulfur or nitrogen, wherein where D is

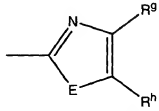
nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen,

wherein

(a) R^c is

(1) Ar,

(2) a group of the formula II,



II

wherein E is sulfur, oxygen, or N-R^i, and R^g, R^h and R^i are independently the same as R^a, R^b and R^d, respectively,

(3) a C_3-C_8 cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cyloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl-, alkoxycarbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-substituents;

(4) a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings;

(5) hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, a group Ar^Φ which is C_6- or C_{10}- aryl or a 5- or 6-membered, or 9- or 10-membered heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar^Φ-alkyl; and

(b) R^f is independently hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, Ar^Φ, or Ar^Φ-alkyl;

wherein aryl, Ar, or Ar^Φ can be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl,

alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, ArO-, Ar-, Ar-alkyl-, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, piperidin-1-yl; and

heterocycles, except those of Ar and Ar^{Φ}, can be substituted with in addition to any substitutions specifically noted one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1 to C_3)alkylenedioxy, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, oxo, sulfamoyl, trifluoromethyl, 4-[C_6 or C_{10}]arylpiperidin-1-yl and 4-[C_6 or C_{10}]arylpiperazin-1-yl- ;

or a pharmaceutically acceptable salt of said compounds,

with the proviso that where the compound of formula I is administered to decrease intraocular pressure at least one compound of formula I administered in effective amount is not a thiazole substituted on a ring carbon sulfonamide (the amide of which can be substituted) that has carbonic anhydrase inhibiting activity.

2. (Original) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein the bond between carbons 4 and 5 is a single bond.

3. (Original) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein R^c is amino, amino(C_1-C_5)alkyl, or amino(C_6 or C_{10})aryl, or wherein the amino of any of the three groups can be substituted with

(a) Ar;

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z- , wherein Z is a carbonyl or -SO_2-; or

(c) formyl or alkanoyl.

4. (Original) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein J is S or O, and R^c is hydrogen, oxo, alkyl, amino,

amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with

(a) Ar;

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z-, wherein Z is a carbonyl or -SO_2-; or

(c) formyl or alkanoyl.

5. (Original) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein J is S, and R^c is hydrogen, oxo, alkyl, amino, amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with

(a) Ar;

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z-, wherein Z is a carbonyl or -SO_2-; or

(c) formyl or alkanoyl.

6. (Original) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein the compound is selected from the group consisting of thiazole, 2-amino-4-chlorobenzothiazole, 2,4,5-trimethylthiazole, 2-(3,5-dimethylphenoxy)-N-thiazol-2-yl)acetamide-, 2-isobutylthiazole, (4-fluorophenyl)thiazolin-2-ylamine, 2-furyl-N-[4-(6-methylbenzothiazol-2-yl)phenyl]carboxamide, and 5,5-dimethyl-2-(2-naphthylamino)-4,5,6-trihydrobenzothiazol-7-one.

7. (Presently Amended) The method of claim 1, comprising administering an effective amount of a compound of the formula I, wherein

~~d.~~ R^a and R^b are

1. independently selected from hydrogen, acylamino, alkanoyl, alkanoylalkyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, piperazin-1-yl, Ar {wherein, consistent with the rules

of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a substituted benzene, pyridine, pyrimidine, pyridazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, ArO-, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-; or

2. together with their ring carbons form a C_6- or C_{10}- aryl fused ring; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having no double bonds except a fused double bond of the formula I or IA ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, amino, aminocarbonyl, carboxy, fluoro, or oxo, where multiple substituents are located on different carbon atoms of the cycloalkyl ring, except in the case of alkyl and fluoro substituents, which can be located on the same or different carbon atoms; or

4. together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or

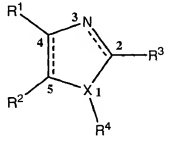
5. together with their ring carbons form a fused five to six membered second heterocycle, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, and $S(O)_n$, wherein n is 1 or 2,

wherein aryl, Ar, or Ar^{Φ} can be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group of alkyl, amino, dialkylamino, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, piperidin-1-yl; and

heterocycles, except those of Ar and Ar^{Φ}, can be substituted with in addition to any substitutions specifically noted one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1 or C_3)alkylenedioxy, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, oxo, sulfamoyl, trifluoromethyl, 4-[C_6 or C_{10}]arylpiperidin-1-yl and 4-[C_6 or C_{10}]arylpiperazin-1-yl, wherein multiple substituents are

located on different atoms of the heterocyclic ring, with the proviso that alkyl, alkoxycarbonyl, and fluoro substituents can be substituted on the same carbon atom of the heterocyclic ring.

8. (Presently Amended) A method of, in an animal, including a human, treating (i) diabetes or treating or ameliorating (ii) adverse sequelae of diabetes, (iii) kidney damage, (iv) damage to blood vasculature, atherosclerosis, peripheral vascular disease, coronary heart disease or heart failure, (v) hypertension, (vi) retinopathy, (vii) peripheral neuropathy, (viii) cataracts, (ix) osteoarthritis, (x) rheumatoid arthritis, (xi) Alzheimer's disease, (xii) damage to a tissue caused by contact with elevated levels of reducing sugars or (xiii) stroke, or (xiv) improving the elasticity or reducing wrinkles of the skin of an animal or (xv) increasing RBC deformability, comprising inhibiting the formation of, or reversing the preformation of, advanced glycosylation end products by administering an effective amount of a compound of formula III:



III

wherein:

X is nitrogen or sulfur, provided that R^4 is present only when X is nitrogen; the carbon 2 to nitrogen bond is a double bond except when R^3 is oxo; the bond between carbons 4 and 5 is a single bond or a double bond;

R^1 and R^2

are independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl, or

together with their ring carbons form a C_6-C_{10} aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, with the proviso that when X is nitrogen R^1 and R^2 do not form a C_6 fused aromatic ring, or

together with their ring carbons form a C_5-C_7 fused cycloalkyl or cycloalkenyl ring having up to two double bonds including a fused double bond of the thiazole radical, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

R^4 is lower alkyl, lower alkenyl or Ar; and

R^3 is

(a) when X is S, R^3 is hydrogen, oxo, alkyl, amino, amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with:

(i) Ar,

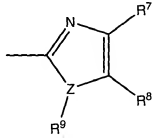
(ii) Ar-carbonyl, Ar-alkanoyl, Ar-carbonylalkyl, Ar-aminocarbonyl Ar-aminoalkanoyl or Ar-oxyalkanoyl or

(iii) formyl or alkanoyl,

(b) -$NHC(O)(CH_2)_n$-Y-R^5R^6, wherein Y is oxygen, sulfur or nitrogen, n is 0 or 1, but n=1 when Y is oxygen or sulfur, and R^6 is present only when Y is nitrogen, wherein R^5 is

(i) Ar,

(ii) a group of the formula:



IV

wherein R^7, R^8 and R^9 are independently the same as R^1, R^2 and R^4, Z is sulfur or nitrogen, R^9 is present only when Z is nitrogen;

(iii) a C_3-C_8 cycloalkyl or cycloalkenyl ring having up to one double bond, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

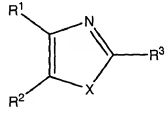
(iv) a 3 to 8-membered heterocyclic ring wherein the heteroatom is one oxygen, one sulfur or one nitrogen, which heterocyclic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups,

(i v) hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl,

and R^6 is independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl;

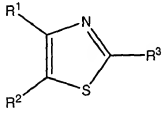
wherein each group Ar can be substituted by one or more halo, amino, alkyl, alkoxy, alkoxycarbonyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, or a pharmaceutically acceptable salt of said compounds.

9. (Original) The method of claim 8, comprising administering an amount effective therefor of one or more compounds of the following formula:



V

10. (Original) The method of claim 8, comprising administering an amount effective therefor of one or more compounds of the following formula:



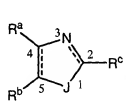
VI

wherein R^1, R^2 and R^3 are defined in claim 1.

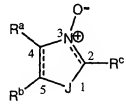
11. (Original) The method of claim 8, comprising administering an amount effective therefor of one or more compounds of formula III, wherein each Ar or cycloalkyl group is substituted

with up to two substituents.

12. (Original) A method of, in an animal, including a human, reducing tissue damage caused by dialysis, comprising, in peritoneal dialysis, administering with a dialysis composition an effective amount of a compound of formula I or IA, or, in hemodialysis, providing in an exchange fluid an effective amount of a compound of formula I or IA, wherein compounds of formula I or IA are as follows:



I **or**



IA

wherein:

a. J is oxygen, sulfur, or N-R^d;

b. the carbon 2 to nitrogen bond is a double bond except when R^c is oxo;

c. the bond between carbons 4 and 5 is a single bond or a double bond;

d. R^a and R^b are

3. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, (ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, piperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a substituted benzene, pyridine, pyrimidine, pyridazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, ArO-, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-

Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R^1 and R^2 comprise methylenedioxy-; or

2. together with their ring carbons form a C_6- or C_{10}- aryl fused ring; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including a fused double bond of the containing group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or

5. together with their ring carbons form a fused five to eight membered second heterocycle, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen., sulfur, and $S(O)_n$, wherein n is 1 or 2;

b. R^d is alkyl, alkenyl, hydrogen, or Ar;

c. R^c is

1. oxo (when $\Delta^{2,3}$ is not present), or (when $\Delta^{2,3}$ is present) hydrogen, alkyl, alkylthio, hydrogen, mercapto, amino, amino(C_1-C_5)alkyl, amino(C_6 or C_{10})aryl, or wherein the amino of the last three groups can be substituted with

(a) Ar,

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z- , wherein Z is a carbonyl or -SO_2-

(c) formyl or alkanoyl, or

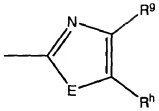
(d) up to two alkyl,

2. -NHC(O)(CH_2)n-D-R^eR^f, wherein D is oxygen, sulfur or nitrogen, wherein where D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=l or 2, and R^f is present only when D is nitrogen, wherein

(a) R^e is

(1) Ar,

(**2**) a group of the formula:



II

wherein E is sulfur, oxygen, or N-R^i, and R^g, R^h and R^i are independently the same as R^a, R^b and R^d, respectively,

(**3**) a C_3-C_8 cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cyloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl-, alkoxycarbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-substituents;

(**4**) a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings;

(**5**) hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, a group Ar^{Φ} which is C_6- or C_{10}- aryl or a 5- or 6-membered, or 9- or 10-membered heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar^{Φ}-alkyl; and

(**b**) R^f is independently hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, Ar^{Φ}, or Ar^{Φ}-alkyl;

wherein aryl, Ar, or Ar^{Φ} can be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, .omega.-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, ArO-, Ar-, Ar-alkyl-, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4- [C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl,

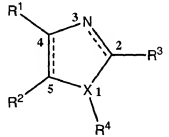
piperazin-1-yl, piperidin-1-yl; and

heterocycles, except those of Ar and Ar^{Φ}, can be substituted with in addition to any substitutions specifically noted one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1 to C_3)alkylenedioxy, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, oxo, sulfamoyl, trifluoromethyl, 4-[C_6 or C_{10}]arylpiperidin-1-yl and 4-[C_6 or C_{10}]arylpiperazin-1-yl- ;

or a pharmaceutically acceptable salt of said compounds,

with the proviso that where the compound of formula I is administered to decrease intraocular pressure at least one compound of formula I administered in effective amount is not a thiazole substituted on a ring carbon sulfonamide (the amide of which can be substituted) that has carbonic anhydrase inhibiting activity.

13. (Original) A method of, in an animal, including a human, reducing tissue damage caused by dialysis, comprising, in peritoneal dialysis, administering with a dialysis composition an effective amount of a compound of formula III, or, in hemodialysis, providing in an exchange fluid an effective amount of a compound of formula III, wherein compounds of formula III are as follows:



III

wherein:

X is nitrogen or sulfur, provided that R^4 is present only when X is nitrogen; the carbon 2 to nitrogen bond is a double bond except when R^3 is oxo; the bond between carbons 4 and 5 is a single bond or a double bond;

R^1 and R^2

are independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9)

heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl, or

together with their ring carbons form a C_6-C_{10} aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, with the proviso that when X is nitrogen R^1 and R^2 do not form a C_6 fused aromatic ring, or

together with their ring carbons form a C_5-C_7 fused cycloalkyl or cycloalkenyl ring having up to two double bonds including a fused double bond of the thiazole radical, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

R^4 is lower alkyl, lower alkenyl or Ar; and

R^3 is

(a) when X is S, R^3 is hydrogen, oxo, alkyl, amino, amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with:

(i) Ar,

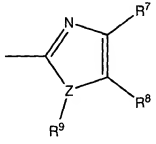
(ii) Ar-carbonyl, Ar-alkanoyl, Ar-carbonylalkyl, Ar-aminocarbonyl Ar-aminoalkanoyl or Ar-oxyalkanoyl or

(iii) formyl or alkanoyl,

(b) -$NHC(O)(CH_2)_n$-Y-R^5R^6, wherein Y is oxygen, sulfur or nitrogen, n is 0 or 1, but n=1 when Y is oxygen or sulfur, and R^6 is present only when Y is nitrogen, wherein R^5 is

(i) Ar,

(ii) a group of the formula:



IV

wherein R^7, R^8 and R^9 are independently the same as R^1, R^2 and R^4, Z is sulfur or nitrogen, R^9 is present only when Z is nitrogen;

(iii) a C_3-C_8 cycloalkyl or cycloalkenyl ring having up to one double bond,

which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

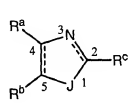
(iv) a 3 to 8-membered heterocyclic ring wherein the heteroatom is one oxygen, one sulfur or one nitrogen, which heterocyclic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups,

(iv) hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl,

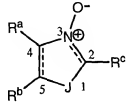
and R^6 is independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl;

wherein each group Ar can be substituted by one or more halo, amino, alkyl, alkoxy, alkoxycarbonyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, or a pharmaceutically acceptable salt of said compounds.

14. (Original) A method of, in an animal, including a human, decreasing or ameliorating bone loss comprising administering an effective amount of a compound of formula I or IA:



I **or**



IA

wherein:

a. J is oxygen, sulfur, or N-R^d;

b. the carbon 2 to nitrogen bond is a double bond except when R^c is oxo;

c. the bond between carbons 4 and 5 is a single bond or a double bond;

d. R^a and R^b are

4. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, .omega.-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, piperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a substituted benzene, pyridine, pyrimidine, pyridazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, ArO-, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R^1 and R^2 comprise methylenedioxy-; or

2. together with their ring carbons form a C_6- or C_{10}- aryl fused ring; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including a fused double bond of the containing group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or

5. together with their ring carbons form a fused five to eight membered second heterocycle, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, and $S(O)_n$, wherein n is 1 or2;

b. R^d is alkyl, alkenyl, hydrogen, or Ar;

c. R^c is

1. oxo (when $\Delta^{2,3}$ is not present), or (when $\Delta^{2,3}$ is present)

(a) Ar,

(b) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z- , wherein Z is a carbonyl or $-SO_2-$

(c) formyl or alkanoyl, or

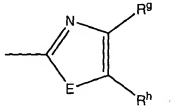
(d) up to two alkyl,

2. $-NHC(O)(CH_2)_n-D-R^eR^f$, wherein D is oxygen, sulfur or nitrogen, wherein where D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen, wherein

(a) R^e is

(1) Ar,

(2) a group of the formula:



II

wherein E is sulfur, oxygen, or N-R^i, and R^g, R^h and R^i are independently the same as R^a, R^b and R^d, respectively,

(3) a C_3-C_8 cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cyloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl-, alkoxycarbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-substituents;

(4) a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings;

(5) hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, a group Ar.sup..phi. which is C_6- or C_{10}- aryl or a 5- or 6-membered, or 9- or 10-membered heteroaryl (wherein

the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar.sup..phi.-alkyl; and

(b) R^f is independently hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, Ar^Φ, or Ar^Φ-alkyl;

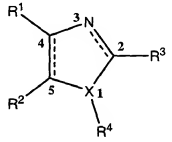
wherein aryl, Ar, or Ar^Φ can be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, .omega.-alkylenesulfonic acid, alkylthio, (allyl, amino, ArC(O)-, ArC(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, ArO-, Ar-, Ar-alkyl-, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, piperidin-1-yl; and

heterocycles, except those of Ar and Ar^Φ, can be substituted with in addition to any substitutions specifically noted one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1 to C_3)alkylenedioxy, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, oxo, sulfamoyl, trifluoromethyl, 4-[C_6 or C_{10}]arylpiperidin-1-yl and 4-[C_6 or C_{10}]arylpiperazin-1-yl- ;

or a pharmaceutically acceptable salt of said compounds,

with the proviso that where the compound of formula I is administered to decrease intraocular pressure at least one compound of formula I administered in effective amount is not a thiazole substituted on a ring carbon sulfonamide (the amide of which can be substituted) that has carbonic anhydrase inhibiting activity.

15. (Original) A method of, in an animal, including a human, decreasing or ameliorating bone loss comprising administering an effective amount of a compound of formula III:



III

wherein:

X is nitrogen or sulfur, provided that R^4 is present only when X is nitrogen; the carbon 2 to nitrogen bond is a double bond except when R is oxo; the bond between carbons 4 and 5 is a single bond or a double bond;

R^1 and R^2

are independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl, or

together with their ring carbons form a C_6-C_{10} aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, with the proviso that when X is nitrogen R^1 and R^2 do not form a C_6 fused aromatic ring, or

together with their ring carbons form a C_5-C_7 fused cycloalkyl or cycloalkenyl ring having up to two double bonds including a fused double bond of the thiazole radical, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

R^4 is lower alkyl, lower alkenyl or Ar; and

R^3 is

(a) when X is S, R^3 is hydrogen, oxo, alkyl, amino, amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with:

(i) Ar,

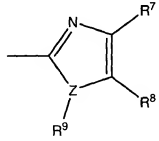
(ii) Ar-carbonyl, Ar-alkanoyl, Ar-carbonylalkyl, Ar-aminocarbonyl Ar-aminoalkanoyl or Ar-oxyalkanoyl or

(iii) formyl or alkanoyl,

(b) -$NHC(O)(CH_2)_n$-Y-R^5R^6, wherein Y is oxygen, sulfur or nitrogen, n is 0 or 1, but n=l when Y is oxygen or sulfur, and R^6 is present only when Y is nitrogen, wherein R^5 is

(i) Ar,

(ii) a group of the formula:



IV

wherein R^7, R^8 and R^9 are independently the same as R^1, R^2 and R^4, Z is sulfur or nitrogen, R^9 is present only when Z is nitrogen;

(iii) a C_3-C_8 cycloalkyl or cycloalkenyl ring having up to one double bond, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

(iv) a 3 to 8-membered heterocyclic ring wherein the heteroatom is one oxygen, one sulfur or one nitrogen, which heterocyclic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups,

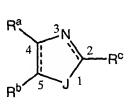
(iv) hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl, and

R^6 is independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9)

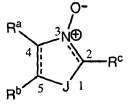
heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl;

wherein each group Ar can be substituted by one or more halo, amino, alkyl, alkoxy, alkoxycarbonyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, or a pharmaceutically acceptable salt of said compounds.

16. (Original) A method of, in an animal, including a human, treating or ameliorating sickle cell disease comprising administering an effective amount of a compound of formula I or IA:



I **or**



IA

wherein:

a. J is oxygen, sulfur, or N-R^d;

b. the carbon 2 to nitrogen bond is a double bond except when R^c is oxo;

c. the bond between carbons 4 and 5 is a single bond or a double bond;

d. R^a and R^b are

5. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, .omega.-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, piperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a substituted benzene, pyridine, pyrimidine, pyridazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon

double bond of Ar)}, Ar-alkyl, ArO-, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R^1 and R^2 comprise methylenedioxy-; or

2. together with their ring carbons form a C_6- or C_{10}- aryl fused ring; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including a fused double bond of the containing group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or

5. together with their ring carbons form a fused five to eight membered second heterocycle, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, and $S(O)_n$, wherein n is 1 or2;

b. R^d is alkyl, alkenyl, hydrogen, or Ar;

c. R^c is

1. oxo (when $\Delta^{2,3}$ is not present), or (when $\Delta^{2,3}$ is present)

(**a**) Ar,

(**b**) Ar-Z-, Ar-alkyl-Z-, Ar-Z-alkyl, Ar-amino-Z-, Ar-aminoalkyl-Z-, or Ar-oxyalkyl-Z- , wherein Z is a carbonyl or -SO_2-

(**c**) formyl or alkanoyl, or

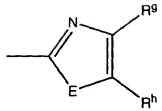
(**d**) up to two alkyl,

2. -$NHC(O)(CH_2)_n$-D-R^eR^f, wherein D is oxygen, sulfur or nitrogen, wherein where D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen, wherein

(**a**) R^e is

(1) Ar,

(2) a group of the formula



II

wherein E is sulfur, oxygen, or N-R^i, and R^g, R^h and R^i are independently the same as R^a, R^b and R^d, respectively,

(3) a C_3-C_8 cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cyloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl-, alkoxycarbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-substituents;

(4) a 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered heteroaryl rings;

(5) hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, a group Ar.sup..phi. which is C_6- or C_{10}- aryl or a 5- or 6-membered, or 9- or 10-membered heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar.sup..phi.-alkyl; and

(b) R^f is independently hydrogen, (C_2-C_6)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, Ar^Φ, or Ar^Φ-alkyl;

wherein aryl, Ar, or Ar^Φ can be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, .omega.-alkylenesulfonic acid, alkylthio, (allyl, amino, ArC(O)-, ArC(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, ArO-

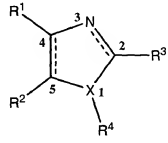
, Ar-, Ar-alkyl-, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, piperidin-1-yl; and

heterocycles, except those of Ar and Ar^{Φ}, can be substituted with in addition to any substitutions specifically noted one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1 to C_3)alkylenedioxy, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, oxo, sulfamoyl, trifluoromethyl, 4-[C_6 or C_{10}]arylpiperidin-1-yl and 4-[C_6 or C_{10}]arylpiperazin-1-yl- ;

or a pharmaceutically acceptable salt of said compounds,

with the proviso that where the compound of formula I is administered to decrease intraocular pressure at least one compound of formula I administered in effective amount is not a thiazole substituted on a ring carbon sulfonamide (the amide of which can be substituted) that has carbonic anhydrase inhibiting activity.

17. (Original) A method of, in an animal, including a human, treating or ameliorating sickle cell disease comprising administering an effective amount of a compound of formula III:



III

wherein:

X is nitrogen or sulfur, provided that R^4 is present only when X is nitrogen; the carbon 2 to nitrogen bond is a double bond except when R is oxo; the bond between carbons 4 and 5 is a single bond or a double bond;

R^1 and R^2

are independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or

Ar-alkyl, or

together with their ring carbons form a C_6-C_{10} aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, with the proviso that when X is nitrogen R^1 and R^2 do not form a C_6 fused aromatic ring, or

together with their ring carbons form a C_5-C_7 fused cycloalkyl or cycloalkenyl ring having up to two double bonds including a fused double bond of the thiazole radical, which aliphatic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

R^4 is lower alkyl, lower alkenyl or Ar; and

R^3 is

(a) when X is S, R^3 is hydrogen, oxo, alkyl, amino, amino(C_1-C_5)alkyl or aminophenyl, wherein the amino of the latter three groups can be substituted with:

(i) Ar,

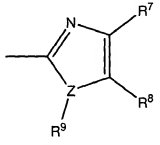
(ii) Ar-carbonyl, Ar-alkanoyl, Ar-carbonylalkyl, Ar-aminocarbonyl Ar-aminoalkanoyl or Ar-oxyalkanoyl or

(iii) formyl or alkanoyl,

(b) $-NHC(O)(CH_2)_n-Y-R^5R^6$, wherein Y is oxygen, sulfur or nitrogen, n is 0 or 1, but n=l when Y is oxygen or sulfur, and R^6 is present only when Y is nitrogen, wherein R^5 is

(i) Ar,

(ii) a group of the formula:



IV

wherein R^7, R^8 and R^9 are independently the same as R^1, R^2 and R^4, Z is sulfur or nitrogen, R^9 is present only when Z is nitrogen;

(iii) a C_3-C_8 cycloalkyl or cycloalkenyl ring having up to one double bond, which aliphatic ring can be substituted by one or more amino, halo, alkyl,

sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups;

(iv) a 3 to 8-membered heterocyclic ring wherein the heteroatom is one oxygen, one sulfur or one nitrogen, which heterocyclic ring can be substituted by one or more amino, halo, alkyl, sulfo, sulfoalkyl, carboxy, carboxyalkyl, or oxo groups,

(iv) hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl, and

R^6 is independently hydrogen, hydroxyalkyl, (C_2-C_6)alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, a group Ar which is (C_6-C_{10}) aryl or (C_5-C_9) heteroaryl (wherein the heteroatom is one oxygen, one sulfur or one nitrogen) or Ar-alkyl;

wherein each group Ar can be substituted by one or more halo, amino, alkyl, alkoxy, alkoxycarbonyl, sulfo, or sulfoalkyl, groups, or a C_1-C_3 alkylenedioxy group, or a pharmaceutically acceptable salt of said compounds.

18. (Previously Canceled).

19. (Previously Canceled).

20. (Previously Canceled).

21. (Previously Canceled).

22. (Canceled).

23. (Previously Canceled).

24. (Canceled).

25. (Previously Canceled).

REMARKS

Upon entry of the present amendment, claims 1-17 are pending in this application. Claims 1-17, 22 and 24 have been rejected. Claims 1, 7 and 8 have been amended. Support for these amendments appears in the specification at, e.g., page 3, lines 3-5. No new matter is added.

Claims 18-21, 23 and 25 were previously cancelled in Paper No. 9 and claims 22 and 24 are cancelled herein as drawn to non-elected inventions. Applicants reserve the right to pursue the subject matter of these claims in a later application.

CLAIM REJECTIONS

Rejections under U.S.C.§ 102

Claims 1 and 4-11 are rejected under 35 U.S.C. § 102(b), as being anticipated by Bru-Magniez et al., U.S. Pat. No. 5,192,781 ("Bru-Magniez"). Applicants respectfully traverse.

Applicants have amended independent claims 1 and 8 to recite "...inhibiting the formation of, or reversing the preformation of, advanced glycosylation end products ..." Support for these amendments can be found throughout the specification and specifically at, e.g., page 3, lines 3-5. Bru-Marniez teaches the synthesis of various thiazaole derivatives and generally teaches their angiotensin II antagonistic properties. However, Bru-Magniez does not teach inhibiting the formation of, or reversing the preformation of, advanced glycosylation end products using the claimed compounds of the present invention.

Thus, Bru-Magniez does not teach or suggest all of the limitations of the claimed invention. Accordingly, Applicants assert that claims 1 and 8, as amended herein, (and claims 4-7 and 9-11, which depend from claims 1 and 8, respectively) are not anticipated by Bru-Magniez. Therefore, this rejection of these claims should be withdrawn.

Rejections under U.S.C.§ 112, second paragraph

Claims 22 and 24 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants have cancelled claims 22 and 24 and therefore this rejection is now moot and should be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested. If there are any questions regarding this application that can be handled in a phone conference with Applicants' Attorneys, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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